PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4 -30746A/SCR		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07742	14/10/1999	16/10/1998
International Patent Classification (IPC) or national classification and IPC		
C07K14/00		
Applicant		
NOVARTIS AG et.al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/05/2000	05.02.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Julia, P Telephone No. +49 89 2399 8410

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07742

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-38 as originally filed

Claims, No.:

1-21 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-21 (partial).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☒ no international search report has been established for the said claims Nos. 1-21 (partial).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-21 (partial).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-21
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-21

Industrial applicability (IA)	Yes:	Claims	1-13,19-21
	No:	Claims	14-18 (see Citations and Explanations)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Additional r marks to item I :

A "Sequence Listing" has been filed with the letter of 26.01.00. This "Sequence Listing" comprises SEQ ID No.: 1 to SEQ ID No.: 122 (pages 1-39) and it does not form part of the application (Rule 13ter.1(f) PCT).

2. Additional remarks to item II :

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (16.10.98).

3. Additional remarks to item III :

As far as the first group of inventions (SEQ ID No.: 1) (see below under "Additional remarks under item IV") is the only group of inventions searched and the (incomplete) International Search Report only concerns this group of inventions, this IPER will only concern said first group of inventions.

4. Additional remarks to item IV :

The IPEA agrees with the non-unity objection originally raised by the International Search Agency (ISA) (**Rule 13 PCT**). The following of inventions have been identified :

i) **claims 1-21 (partial) :** an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 1; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides having the sequence of any of SEQ ID No.: 2-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 1; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof.

ii) **claims 1-21 (partial) :** the same as the first group of inventions but for SEQ ID No.: 2.

iii) **claims 1-21 (partial) :** the same as the first group of inventions but for SEQ ID No.: 3.

iv) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 4.

v) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 5.

vi) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 6.

vii) claims 1-21 (partial): the same as the first group of inventions but for SEQ ID No.: 7.

viii) claims 1-21(partial): the same as the first group of inventions but for SEQ ID No.: 8.

ix) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 9.

x) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 10.

xi) claims 1-21 (partial) : the same as the first group of inventions but for SEQ ID No.: 11.

xii) claims 1-21 (partial): the same as the first group of inventions but for SEQ ID No.: 12.

xiii) claims 1-21(partial): the same as the first group of inventions but for SEQ ID No.: 13.

xiv) claims 1-21(partial): the same as the first group of inventions but for SEQ ID No.: 14.

xv) claims 1-21 (partial): the same as the first group of inventions but for SEQ ID No.: 15.

xvi) claims 1-21(partial): the same as the first group of inventions but for SEQ ID No.: 16.

According to **Rule 13 PCT** an application must relate only to one invention or to a group of inventions so linked as to form a **single inventive concept**, i.e. having at least one common technical feature defining a contribution over the known prior art. In the present case, the common technical feature among the different identified groups of inventions seems to be their ability to bind target nucleotides of the formula 5'-(GNN)-3'. However, the binding of different zinc finger-nucleotide binding polypeptides to target nucleotides of the formula 5'-(GNN)-3' was already well-known in the prior art. In particular, the document WO96/06166 on Figure 6 discloses different alpha-helix sequences with the ability to bind to target nucleotides of the formula 5'-(GNN)-3' including the sequence

"QQSNLVR(HQR)"with high specificity for "GAT". This document also discloses the possible combination of different zinc finger polypeptides for targeting desired DNA sequences (page 9).

The technical problem underlying the present application is considered to be the provision of alternative zinc finger-nucleotide binding polypeptides with the ability to bind to 5'-(GNN)-3' and the combination thereof. This problem is solved by each of the different groups of inventions above identified. However, in view of their different primary structure and binding specificity (see figure 1 of the present application), the IPEA, in agreement with the ISA, fails to see which is the single common technical feature defining an inventive contribution over the known prior art.

Thus, the IPEA maintains the non-unity objection originally raised by the ISA (Rule 13 PCT) and this IPER will only concern the first group of inventions (i.e. SEQ ID No.: 1) (see "Additional remarks under item III").

5. Additional remarks to item V :

The present application discloses different zinc finger-nucleotide binding polypeptides having binding specificity for target nucleotides containing one or multiple 5'-(GNN)-3' triplets. The application shows that with a family of defined zinc finger domains (heptamer within the alpha-helical domain of the polypeptide) recognizing sequences of the 5'-(GNN)-3' subset of a 64 member zinc finger alphabet (figure 1 and particularly Table 1 on page 13), polydactyl proteins specifically recognize novel 9-bp or 18-bp sequences. The application is exemplified by the production of a designed three and six (zinc)-finger protein (E2C) and derivatives thereof (fusion proteins with effector domains, E2C-KRAB, E2C-VP64, etc...), all being variants of the finger 2 (F2) pmGAC, pmGAG, pGCA, pGCC, etc... (example 4). These products have been used for specifically regulate different genes (erbB-2) in Hela cells, in non-human primate cells and in breast cancer cells.

The following documents have ben cited in the International Search Report (ISR) and they have been found to be relevant for assessing the novelty and inventiveness of the present application :

i) WO96/06166 (**D1**) is concerned with the same technical problem than the present

application. D1 discloses the selection of different nucleotide binding regions and characterizes the amino acid-base (target sequences) in the zinc finger-DNA complexes deduced from phage display (of 3-finger DNA binding-domains) (Zif268 variants). Table 1 (page 23) discloses the sequences with selectivity for eleven different GNN target triplets, including a "QQSNLVR" sequence (specificity for GAT, see Figure 1 of the present application too), wherein a bold letter identifies a different residue in comparison to SEQ ID No.: 1 of the present application. D1 not only refers to the known importance of positions -1, +3 and +6 which was already acknowledged in the prior art but it also emphasizes the importance of position +2 (see Table 2 on page 34) and at least one of positions +1, +5 and +8 (only three primary positions and one auxiliary position are involved in the recognition of DNA). D1 further refers to similar embodiments than the present application including zinc finger-nucleotide binding polypeptides comprising the disclosed nucleotide binding regions (with designed specificity), "compositions" comprising different number and types of the disclosed nucleotide binding regions (fusion polypeptides with the linker of SEQ ID No.: 111, TGEKP, see Figure 7 for instance in D1), polynucleotides encoding said polypeptides and compositions, uses thereof, etc...

ii) a similar disclosure is found in the document Choo and Klug, Proc. Natl. Acad. Sci. USA 1994, Vol. 91, 11163-11167 (**D2**) and the continuing paper Choo and Klug, Proc. Natl. Acad. Sci. USA 1994, Vol. 91, 11168-11172 (**D3**) which correspond to the scientific publication of D1. As a logical following of this work, the document Liu et al., Proc. Natl. Acad. Sci. USA 1997, Vol. 94, 5525-5530 (**D4**) discloses the use of structure-based modelling to design a polypeptide linker (TGEKP) that fuses two three-finger proteins and designs polydactyl zinc-finger proteins with desired (high) selectivity and specificity, i.e. two six-fingered proteins which bind, as in the present application, 18 contiguous bp of DNA in a sequence-specific fashion. Reference is made to the use of these polydactyl proteins for binding DNA sequences with high affinity and specificity and their possible function in human cells to either activate or repress transcription with a possible application in future gene therapy strategies (page 5529, right column).

iii) document Ogawa et al., Cancer Genetics and Cytogenetics 1998, Vol. 1, 36-42 (**D5**) discloses the nucleotide sequence and the corresponding encoded amino acid sequence of a natural human zinc finger protein, namely ZFS-1, isolated from a human seminoma cDNA library. This protein has 13 zinc-finger repeats in its carboxyl terminal region linked by the peptide TGEKP (Figure 1A). Several of these repeats are closely related to the one

of SEQ ID No.: 1 of the present application, such as "QSSNL**IK**", "QSS**HLTT**", "QSS**KLTE**", "QSS**KLTK**", in particular the very closely related "QSSNL**TR**". This last sequence has the same residues at the critical positions -1, +3, and +6 as well as in positions +1, +2 and +4 and it only presents a difference with SEQ ID No.: 1 at position +5 (V/T). This position, however, according to the present application is not critical or essential.

iv) different (18) zinc-finger peptides have also been identified (as EST) in the differentiated exocrine pancreatic cell line AR4IP as shown in the document Gebelein et al.,Cancer Letters 1996, Vol. 105, 225-231 (**D6**). Several of these domains present a close similarity to SEQ ID No.: 1 of the present application, such as "Q**T**SNL**A**R" (DZF1), "Q**K**SNLI**R**" (DZF4 and DZF10), "Q**M**SNLI**R**" (DAF16), etc... all these sequences have two differences, namely at position +1 or +5 and a conservative exchange at position +5 (A/V and I/V). However, the critical positions, namely -1 (Q), +3 (N) and +6 (R), have the same residues as well as in positions +2 (S) and +4 (L).

In view of this prior art, the IPEA considers that the selection of SEQ ID No.: 1 over the closely related sequences disclosed in said prior art is an arbitrary selection among all possible nucleotide binding regions (conservative exchanges or substitutions in non-critical positions of a well-known nucleotide binding region identified in this prior art) and it does not have any surprising technical effect which could amount to an inventive contribution. Thus, even if the specific SEQ ID No.: 1 is novel in the light of this cited prior art (Article 33 (2) PCT), the subject matter of claims 1-21 does not fulfil the requirements of Article 33 (3) PCT.

The attention of the Applicant is also drawn to the fact that the subject matter of claims 14-18 can be seen as directed to methods for treatment of the human or animal body (insofar the claimed subject matter comprises in vivo methods for regulating the expression of a gene containing the indicated nucleotide sequence) and thus, it may be excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT too. Furthermore, for such a subject matter no unified criteria exist in PCT for the assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the

use of such a compound for the manufacture of a medicament for a new medical treatment.

6. Additional remarks to item VIII :

The following objections are also raised under **Article 6 PCT** concerning the clarity of the claims :

i) the subject matter of claim 1 is directed to a product (polypeptide) characterized by a functional property, namely its ability to bind a nucleotide, and a structural one, namely the presence of (a) a zinc-finger domain and (b) a nucleotide binding region having the sequence of any of SEQ ID No.: 1-16. However, there is no requirement that both (a) and (b) must actually be the same domain or region and that the functional property must be the result or achieved by the presence of (b). Thus, any zinc finger-nucleotide binding polypeptide having the given SEQ ID would actually fall under the scope of this claim, even if the ability to bind a nucleotide is not associated to the presence of the given SEQ ID No.

ii) the subject matter of claim 2 is directed to a "composition" which is characterized by the fact that it comprises "from 2 to about 12 of the polypeptide of claim 1". Claim 1 being directed to "an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of any of SEQ ID No.: 1-16". Thus, the scope of claim 2 is ambiguous. Does it actually intend to protect a composition which only has "from 2 to 12" isolated and purified zinc-finger nucleotide binding polypeptides of claim 1 (from 2 to 12 moles, grams??) and thus, including two polypeptides of the same type (containing an identical nucleotide binding region)?? or else does it mean a polypeptide (and not a composition) containing "from 2 to 12" nucleotide binding regions having the sequence of any of SEQ ID No: 1-16 and/or combinations thereof ?? or in view of the wording of claims 4-5 actually means a fusion protein comprising the different polypeptides as fusion partners ???. In view of all these interpretations, the actual meaning of the wording "composition" (mixture of one or more compounds) is in this claim ambiguous. In this respect, the subject matter of claim 11 directed to "an isolated and purified polynucleotide" which encodes a "composition" (mixture of different polynucleotides ??) is also ambiguous (and therefore all related dependent claims).

iii) the meaning of "operatively linked" in claim 4 is ambiguous too as far as said claim

does not clearly indicate any special function (does it intend to mean that the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-16 are still able to bind a nucleotide? or else that the zinc finger-nucleotide binding polypeptide are still able to bind a nucleotide by the presence of other sequences even if the ones of the given SEQ ID No are not functional ???). In this respect and for the same reasons, the same wording in claims 8-9 and 18 is also considered ambiguous.

iv) the presence of the wording "about" in claims 2 and 3 makes their scope of protection ambiguous ("about 12" does it actually includes 15, 16, 20, etc...?? in other words, the scope of the claim is ambiguously open to subjective interpretations).

v) both the wording "regulating" and "exposing" in claim 14 is ambiguous. It is not clear to the IPEA what is actually "regulated" in the context of a nucleotide sequence alone. In fact, it seems to the IPEA that what is actually regulated is the transcription, expression, etc... of a particular nucleotide sequence but not such a sequence "per se". Moreover, the fact that "exposing" the nucleotide sequence and the composition is not sufficient for a successful regulation. Under certain conditions of pH, temperature, buffer composition, etc... such "exposure" will not result in any "binding" and thus, no regulation will be achieved. Said "exposure" must be further defined as being carried out under suitable conditions for allowing the above referred binding.

vi) whereas the application of zinc finger-nucleotide binding polypeptides in the regulation of gene transcription by interaction with the corresponding nucleotide sequences in the promoter region of said gene (gene switching) is a well-known use which have clearly been shown in the prior art and by the examples of the present application, there is no basis for the regulation of gene transcription when the polypeptide may bind a motif within a structural gene or within an RNA sequence different from the promoter region, even more in view of the results shown in the present application (end of page 27 : "... the mechanism of repression is active inhibition of transcription inhibition rather than elongation ... to be readily displaced from the DNA by the action of the polymerase"). Thus, the subject matter of claims 16 and 17 lacks technical support in the present application (Article 6 PCT in combination with Article 5 PCT).

vii) the Applicant is reminded that a claim to a substance for a particular use is construed as meaning a substance or composition which is in fact suitable for the stated use; a

known product which is per se the same as the substance or composition defined in the claim, but which is in a form which would render it unsuitable for the stated use, would not deprive the claim of novelty (PCT International Preliminary Examination Guidelines, as in force from 09.10.98, Section IV, paragraph III-4.8). The subject matter of claim 19 is directed to a product for use as a medicament, i.e. it is worded as a first medical use claim. For such a subject matter no unified criteria exist in PCT. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. In this respect, claims 20 and 21 are worded as second medical claims ("Swiss-type claims"), wherein however claim 20 does not indicate any specific treatment but only a generic one.

viii) the examples of the present application only demonstrate a specific combination of a particular SEQ ID No as well as for compositions thereof but there is no demonstration of the binding selectivity and specificity or affinity for all disclosed nucleotide binding regions (SEQ ID No.) let alone for compositions or combinations thereof. Figure 1 indicates a general specificity without indicating any specific value (see for instance SEQ ID No 1, 5, 12, 15 and 16, wherein reference is made to at least two different target sequences !!!). Table 1 indicates too the sequences showing the highest selectivity but without given any further detailed information (affinity constant and/or dissociation constant, degree of specificity, etc...). In view of the great number of possible combinations with resulting different properties (specificity, affinity), the IPEA considers that the claimed subject matter is only partially (technically) supported by the present description (Article 6 PCT in combination with Article 5 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
4-30746A/SCR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/07742	14/10/1999	16/10/1998
Applicant		
NOVARTIS AG et.al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 99/07742

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 21 (partial)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 1; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 2-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 1; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

2. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 2; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1 or 3-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 2; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

3. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 3; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-2 or 4-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 3; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions; medicament comprising these compositions and uses thereof

4. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 4; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-3 or 5-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 4; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

5. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 5; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-4 or 6-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 5; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

6. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 6; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-5 or 7-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 6; an isolated and purified

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

7. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 7; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-6 or 8-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 7; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

8. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 8; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-7 or 9-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 8; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

9. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 9; compositions comprising from 2 to about 12 of isolated and purified zinc

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-8 or 10-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 9; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

10. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 10; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-9 or 11-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 10; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

11. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 11; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-10 or 12-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 11; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

12. Claims: 1-21 (partial)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 12; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-11 or 13-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 12; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

13. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 13; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-12 or 14-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 13; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

14. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 14; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-13 or 15-16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 14; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions; medicament comprising these compositions and uses thereof

15. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 15; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-14 or 16 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 15; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

16. Claims: 1-21 (partial)

an isolated and purified zinc finger-nucleotide binding polypeptide that contains a nucleotide binding region having the sequence of SEQ ID No.: 16; compositions comprising from 2 to about 12 of isolated and purified zinc finger-nucleotide binding polypeptides containing the nucleotide binding regions having the sequence of any of SEQ ID No.: 1-15 and wherein at least one of said polypeptides contains the nucleotide binding region having the sequence of SEQ ID No.: 16; an isolated and purified polynucleotide encoding said polypeptide or compositions thereof; expression vectors; a process of regulating a nucleotide sequence that contains 5'-(GNN)n-3', where n is an integer from 1 to 6, the process comprising exposing the nucleotide sequence to an effective amount of these compositions; medicament comprising these compositions and uses thereof

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07742

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/10 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	T. OGAWA ET AL.,: "Enhanced expression in seminoma of human zinc finger genes located on chromosome 19" CANCER GENET. CYTOGENET., vol. 100, no. 1, 1 January 1998 (1998-01-01), pages 36-42, XP000882080 * page 37, right column, last full-paragraph; figure 1A * --- -/--	1-11, 19-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2000	23. 06. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Julia, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	B. GEBELEIN ET AL.,: "A novel profile of expressed tags for zinc finger encoding genes from the poorly differentiated exocrine pancreatic cell line AR4IP" CANCER LETT., vol. 105, no. 2, 2 August 1996 (1996-08-02), pages 225-231, XP000882088 * whole document, in particular Table 1 *	1-11, 19-21
A	CHOO Y ET AL: "Selection of DNA binding sites for zinc fingers using rationally randomized DNA reveals coded interactions" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, 8 November 1994 (1994-11-08), pages 1168-1172, XP002075339 ISSN: 0027-8424 cited in the application * whole document, in particular figure 1 and page 11172, left-column, last paragraph to right-column, last paragraph *	1-21
A	CHOO Y ET AL: "Toward a code for the interactions of zinc fingers with DNA: Selection of randomized fingers displayed on phage" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, 8 November 1994 (1994-11-08), pages 1163-1167, XP002075340 ISSN: 0027-8424 cited in the application * whole document, in particular figure 2 *	1-21
Y	WO 96 06166 A (MEDICAL RES COUNCIL ;CHOO YEN (SG); KLUG AARON (GB); GARCIA ISIDRO) 29 February 1996 (1996-02-29) * whole document, in particular Table 1 and figures 4 and 7 *	1-21
Y	Q. LIU ET AL.,: "Design of polydactyl zinc-finger proteins for unique addressing within complex genomes" PROC. NATL. ACAD. SCI. USA, vol. 94, May 1997 (1997-05), pages 5525-5530, XP002918175 cited in the application * whole document, in particular page 5529, right-column *	1-21

INTERNATIONAL SEARCH REPORT

Infor on patent family members

International Application No
PC[redacted]EP 99/07742

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606166 A	29-02-1996	AU 1003799 A	22-04-1999
		AU 698152 B	22-10-1998
		AU 3229195 A	14-03-1996
		CA 2196419 A	29-02-1996
		EP 0781331 A	02-07-1997
		JP 10504461 T	06-05-1998
		US 6013453 A	11-01-2000
		US 6007988 A	28-12-1999

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB95/01949

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 36 completely and (29-35 are partially as far as they concern an in vivo treatment) is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 June 2000 (06.06.00)	
International application No. PCT/EP99/07742	**Applicant's or agent's file reference** 4 -30746A/SCR
International filing date (day/month/year) 14 October 1999 (14.10.99)	**Priority date** (day/month/year) 16 October 1998 (16.10.98)
Applicant BARBAS, Carlos, F.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 May 2000 (11.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
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